

**REMARKS**

Upon entry of the present amendments, claims 1-70 are pending in this application. Claims 1, 10, 14, 18, 22, 28, 34, 40, 50, 51 and 52 have been amended as shown above. Specifically, claim 1 has been amended to recite a proviso that when  $n$  is 0,  $R^2$  is H or  $(C_1-C_4)alkyl$ . Support for this amendment can be found in Table 1, in examples I-28 though I-133, and in the claims as originally filed. Claims 10, 14, 18, 22, 28, 34, 40, 50, 51 and 52 have been amended to remove their dependency on claim 1. Claim 52 has been amended to recite "a method for modulating the production or proliferation of T-cells." Support for this amendment can be found throughout the specification, e.g., at page 2, lines 20 through page 3, line 8. Support for newly added claims 68-70 can be found at Page 1, lines 16-20 and at page 87, lines 16-27. No new matter has been added. Applicants reserve their rights to prosecute the subject matter of any canceled claim in one or more continuation, continuation-in-part, or divisional applications.

**The Rejection under 35 U.S.C. § 112, First Paragraph Should be Withdrawn**

Claims 49-52 and 64-67 stand rejected under 35 U.S.C. § 112 first paragraph. In particular, the full scope of the claims is allegedly not enabled. Applicants respectfully traverse this rejection for the following reasons.

As the Examiner is aware, patents preferably omit what is well known in the art. Manual of Patent Examining Procedure ("M.P.E.P"), § 2164.01 (8th ed., August 2001). Consequently, "the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *Id.* (quoting *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988)). Furthermore, experimentation is not "undue" simply because it may be complex, expensive, or time-consuming. *Id.*, §§ 2164.01 and 2164.06 (citing, for example, *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); *In re Colianni*, 561 F.2d 220, 224 (CCPA 1977); *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988)).

Claims 49-52 and 64-67 are directed, in part, to methods of modulating the production of certain cytokines and T-cells. Modulation is a term well-known in the art which, unlike the definition asserted by the examiner, does not require the simultaneous enhancement and inhibition of an activity by a single compound. See, e.g., *Stedman's*

*Medical Dictionary* (27<sup>th</sup> Ed.). According to the claimed methods, modulation is achieved by administering a compound of the invention to a mammal or mammalian cell. This can be readily accomplished by those of ordinary skill in the art, as Applicants have fully described how to synthesize compounds of the invention. *See e.g.*, page 70 line 1 through page 77, line 33. Applicants have also fully described methods of administering compounds of the invention. *See e.g.*, page 80 line 1 through page 84, line 23. Applicants have further described assays that can be used to determine the biological activity of compounds of the invention, and other means of testing the compounds to modulate TNF- $\alpha$ , IL-1 $\beta$ , IL-10 or T-cell production are well known to those of ordinary skill in the art. Thus, one of ordinary skill in the art would be able to make and use the claimed invention with no or merely routine experimentation. For this reason, Applicants respectfully request that the rejection of claims 49-52 and 64-67 be withdrawn.

**The Rejection under 35 U.S.C. § 102(b) Should be Withdrawn**

Claims 1, 4, 6, 9, 10, 12, 14, 16, 18, 20, 22, 24, 25, 28, 30, 34, 36, 37 and 40 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by International Patent Publication WO 98/54170 to Muller et al. ("Muller"). Applicants respectfully traverse this rejection for the following reasons.

A prior art reference must disclose all of the limitations of a claim in order to anticipate that claim. *See* M.P.E.P. § 2131. There must be no difference between the claimed invention and the reference disclosure as viewed by one of ordinary skill in the art. *Scripps Clinic & Research Fdn. v. Genentech*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). Put another way, "[a] claim is anticipated and therefore invalid only when a single prior art reference discloses *each and every* limitation of the claim." *Glaxo Inc. v. Novapharm Ltd.*, 52 F.3d 1043, 1047, cert. denied, 116 S. Ct. 516 (1995) (citations omitted) (emphasis added).

In the event a reference does not explicitly teach all elements of a claim, anticipation can only be shown by inherency if, and only if, the cited reference makes it clear that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by one of ordinary skill in the art. *In re Robertson*, 169 F.3d 743, 49 U.S.P.Q.2d 1949 (Fed. Cir. 1999) (citing *Continental Can Company USA Inc. v. Monsanto Company*, 948 F.2d 1264 (Fed. Cir. 1991)). Consequently, inherency cannot be established by probabilities or possibilities: "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient to support an

assertion of inherency." *In re Oelrich*, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981) (quoting *Hansgirk v. Kemmer*, 102 F.2d 212, 414 (C.C.P.A. 1939)). Therefore, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." M.P.E.P. § 2112, citing *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (*Bd. Pat. App. & Inter.* 1990).

Claim 1 has been amended to recite a proviso that when  $n$  is 0,  $R^2$  is H or (C<sub>1</sub>-C<sub>4</sub>)alkyl, and claims 10, 14, and 18 have been amended to remove their dependency on claim 1. These, and the other pending dependent claims do not read on Formula IIB of Muller. Formula IIB requires the-NHR<sup>5</sup> moiety be bound directly to the benzene functionality. The compounds of claim 1, when  $n$  is not 0, and claims 10, 12, 14, 16, 18, and 20, all have a methylene group between the benzene functionality and the-NHR moiety. Therefore, Muller does not disclose of all the limitations of the pending claims.

Claims 22, 28, and 34 have been amended to remove their dependency on claim 1. Claims 1, 22, 24, 25, 28, 30, 34, 36, and 37 do not read on Formula IIB of Muller. Formula IIB discloses compounds where  $R^6$  is alkyl of 1 to 8 carbon atoms, benzo, chloro or fluoro. Claim 1, when  $n$  is 0, and claims 22, 24, 25, 28, 30, 34, 36, and 37, recite compounds where  $R^2$  is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl. Therefore, Muller does not disclose all of the limitations of claims 1, 22, 24, 25, 28, 30, 34, 36, and 37, and cannot anticipate the instant claims.

Finally, claim 40 has been amended to remove its dependency on claim 1. No compound of Muller anticipates instant Claim 40. Applicants therefore respectfully request the rejection under 35 U.S.C. §102(b) be withdrawn.

#### **The Rejection under 35 U.S.C. § 103(a) Should be Withdrawn**

Claims 1-67 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over United States Patent No. 5,635,517 ("the '517 patent") in view of Muller, *Design of Prodrugs* by Hans Bundgaard ("Bundgaard"), Naik CA 118 ("Naik") and WO 97/45117 to Smith et al. ("Smith"). Applicants respectfully traverse the rejection for the reasons discussed below.

In order to properly determine a *prima facie* case of obviousness, an examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P.

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§2142. This is important, as "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." *Id.* Three basic criteria must then be met: first, there must be some suggestion or motivation to modify or combine the cited references; second, there must be a reasonable expectation of success; and third, the prior art references must teach or suggest all the claim limitations. *Id.* at § 2143. With regard to the first criterion, it is important to recognize that the "mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *Id.* at 2143.01 (citing *In re Mills*, 916 F.3d 680 (Fed. Cir. 1990)).

Claims 1-67 relate to compounds, compositions and methods of treatment using a novel class of isoindole-imide compounds. The '517 patent relates to a distinct class of isoindole-imide compounds. In fact, the Examiner has admitted that the compounds of the '517 patent are not encompassed by the present application. See, Office Action, page 3. However, the Examiner alleges that the claimed compounds are prodrugs of compounds of the '517 patent, and that the preparation of prodrugs is well known in the art as evidenced by Bungaard, Naik and Smith. The Examiner, also alleges that the compounds of the present invention are prodrugs of thalidomide, and that one of skill in the art would be motivated to make a prodrug of thalidomide to avoid its adverse effects. Applicants respectfully disagree.

First, Applicants respectfully submit that the assertion that the presently claimed compounds are prodrugs of the compounds of the '517 patent is entirely without factual support.<sup>1</sup>

Second, while Bungaard does describe the formation of prodrugs generally, and Naik describes specific prodrugs of azidoprofen esters, nowhere does the '517 patent alone or in combination with Muller, Bungaard, Naik or Smith suggest modifying the compounds of the '517 patent in the specific manner necessary to obtain the compounds of the invention. Even if, for the sake of argument, the combination did support such a modification, it would not have provided those of ordinary skill in the art with a reasonable expectation of successfully obtaining the claimed invention. See *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). This is because the cited references do not teach or suggest that this modification would be effective in modulating the production of TNF- $\alpha$ ,

<sup>1</sup> To the extent these assertions are based on the Examiner's personal knowledge, Applicants respectfully request that such knowledge be supported by an affidavit. 37 C.F.R. §1.104(d)(2)

IL-1 $\beta$ , IL-10, IL-2, or T-cells in treating cancer, inflammatory disorders, or heart disease. Applicants therefore respectfully submit that claims 1-67 are not obvious over the '517 patent alone, or in combination with Muller, Bungard, Naik or Smith, and respectfully request the withdrawal of the rejection.

**The Obvious-Type Double Patenting Rejection Should be Withdrawn**

On page 4 of the Office Action, claims 1-67 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-2 of United States Patent No. 6,395,754 ("the '754" patent) and over claims 1-10 of United States Patent No. 5,635,517 and claims 1-12 of United States Patent No. 6,395,754 in view of Bungard, Naik and Smith. As discussed above, neither the '517 patent nor the specification of WO98/54170, which corresponds to the '754 patent, render the present invention obvious. Consequently, Applicants respectfully request that the obvious-type double patent rejections be withdrawn.

**The Provisional Double Patenting Rejection Should be Withdrawn**

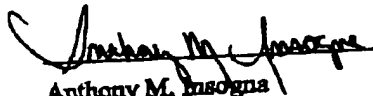
On page 5 of the Office Action, claims 1-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-116 of co-pending United States Patent Application No. 09/972,487. This is a provisional rejection. Consequently, if the Examiner maintains this rejection when the claims are otherwise deemed allowable, Applicants will take the necessary steps to overcome it (e.g., by filing a Terminal Disclaimer).

**Conclusion**

Applicants respectfully request that the above remarks and accompanying documents be entered in the present application file. An early allowance of the present application is respectfully requested.

Respectfully submitted,

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